Vertebral osteomyelitis: clinical features and diagnosis

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Abstract

We aimed to describe clinical and diagnostic features of vertebral osteomyelitis for differential diagnosis and treatment. This is a prospective observational study performed between 2002 and 2012 in Ankara Numune Education and Research Hospital in Ankara, Turkey. All the patients with vertebral osteomyelitis were followed for from 6 months to 3 years. In total, 214 patients were included in the study, 113 out of 214 (53%) were female. Out of 214 patients, 96 (45%) had brucellar vertebral osteomyelitis (BVO), 63 (29%) had tuberculous vertebral osteomyelitis (TVO), and 55 (26%) had pyogenic vertebral osteomyelitis (PVO). Mean number of days between onset of symptoms and establishment of diagnosis was greater with the patients with TVO (266 days) than BVO (115 days) or PVO (151 days, $p < 0.001$). In blood cultures, *Brucella* spp. were isolated from 35 of 96 BVO patients (35%). Among 55 PVO patients, the aetiological agent was isolated in 11 (20%) patients. For tuberculin skin test >15 mm, sensitivity was 0.66, specificity was 0.97, positive predictive value was 0.89, negative predictive value was 0.88, and receiver operating characteristics area was 0.8. Tuberculous and brucellar vertebral osteomyelitis remained the leading causes of vertebral osteomyelitis with delayed diagnosis. In differential diagnosis of vertebral osteomyelitis, consumption of unpasteurized cheese, dealing with husbandry, sweating, arthralgia, hepatomegaly, elevated alanine transaminase, and lumbar involvement in magnetic resonance imaging were found to be predictors of BVO, thoracic involvement in magnetic resonance imaging and tuberculin skin test > 15 mm were found to be predictors of TVO, and history of spinal surgery and leucocytosis were found to be predictors of PVO.

Keywords: *Brucella*, pyogenic, tuberculosis, vertebral osteomyelitis
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Introduction

Vertebral osteomyelitis (VO) is a compelling clinical entity for clinicians, because of its insidious start and indolent course, which make diagnosis difficult. As a consequence, patients often develop destructive lesions or neurological complications related to compression of the spinal cord or its roots [1]. Vertebral osteomyelitis is an infrequent infection; however, the incidence is increasing because of the growing number of older patients and chronic diseases [1]. In many reports VO was grouped as brucellar (BVO), tuberculous (TVO) and pyogenic (PVO) [1,2]. Some studies reported only one clinical entity [3]; however, comparable studies are necessary for differential diagnosis of these disease entities for management of patients.

Diagnostic studies of VO differ according to the prevalence of these diseases. This study was performed in Turkey, where brucellosis and tuberculosis are more common than in European and North American countries. By this prospective study, we aimed to describe clinical and diagnostic features of VO for differential diagnosis and treatment.

Materials and Methods

This is a prospective observational study performed between 2002 and 2012 in Ankara Numune Education and Research Hospital in Ankara, Turkey. Diagnosis of VO was made

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according to clinical, radiological and microbiological criteria, which were defined previously [4,5]. The diagnostic algorithm was performed according to (i) clinical symptoms suggestive of VO, (ii) laboratory abnormalities—complete white blood cell count, erythrocyte sedimentation rate, C-reactive protein level, Brucella tube agglutination test of serum and/or cerebrospinal fluid, tuberculin skin test (TST), (iii) abnormal magnetic resonance imaging (MRI) or computed tomography scan features compatible with infection of the spine, (iv) isolation of the causative microorganism, typical histological pattern from percutaneous disc or epidural abscess puncture or biopsy, and specific tests for microorganisms.

Patients were included if there was illness compatible with vertebral infection and evidence of spinal involvement from imaging. Definite diagnosis of TVO was considered when *Mycobacterium tuberculosis* was isolated from a sample of vertebral, paravertebral or epidural tissue or from a psoas abscess. Probable TVO diagnosis was considered when caseating granulomas, with or without acid-fast bacilli, PCR positivity in a vertebral biopsy and TST positivity were found, or when *M. tuberculosis* was isolated from another focus of infection such as sputum, urine and cerebrospinal fluid. Presumptive diagnosis of TVO was considered when positive findings by imaging, plus positive TST, and no response to non-specific antibiotics but response to anti-tuberculosis treatment were reported. Definite BVO was considered when *Brucella* spp. were isolated from a sample of vertebral, paravertebral or epidural tissue or from a psoas abscess, from blood or other body fluid or tissue specimens, or when *Brucella* standard tube agglutination of >1/160 was found in addition to clinical findings compatible with VO. Definite PVO was considered when a microorganism was isolated from the involved vertebra, intervertebral disc space, or paravertebral or epidural abscesses. Probable PVO was considered when the results of at least two blood cultures were positive during a compatible illness. Presumptive PVO was considered when an organism was isolated from urine, stool and wound, if a sinus tract was detected in contiguity with the vertebral lesions, if there was a history of vertebral surgery, and if empiric antibiotic therapy was successful. For each disease entity, the other two entities were ruled out. All the patients with VO were followed for from 6 months to 3 years. Informed consent was obtained from patients.

Statistical analysis

Chi-square test was used for comparison of categorical variables and *t*-test was used for comparison of continuous variables. Multivariate analysis was performed for detection of the predictors of each disease category separately. Independent variables were selected from the statistically significant variables listed in Tables 1 and 2. In multivariate analysis for the predictors of BVO, consumption of unpasteurized cheese, dealing with husbandry, sweating, arthralgia, hepatomegaly, elevated alanine transaminase, and lumbar involvement in MRI were included in the regression model. In multivariate analysis for prediction of TVO, thoracic involvement in MRI and TST >15 mm were included in the regression model. In multivariate analysis for prediction of PVO, history of spinal surgery and leucocytosis were included in the model. A backward selection process was run. In analysis, STATA version 11 (StatCorp, College Station, TX, USA) was used, and statistical significance was set as $p < 0.005$.

Results

In total, 214 patients were included in the study, 113 (53%) were female. Out of 214 patients, 96 (45%) had BVO, 63 (29%) had TVO and 55 (26%) had PVO. The mean age of the patients with TVO was lower than that of the patients with BVO and PVO (43 versus 53 and 53 years, $p < 0.001$, Table 1). Consumption of fresh cheese and dealing with husbandry, and being a farmer were more commonly reported among the patients with BVO ($p < 0.001$, Table 1). Diabetes mellitus was more common among patients with PVO (33%) than patients with BVO (15%) or TVO (33%, p 0.028, Table 1). The history of spinal surgery was more common among the patients with PVO (64%) than the patients with BVO (11%) or TVO (13%, $p < 0.001$, Table 1).

Fever as a symptom or sign was not statistically different among the three groups; however, sweating was more common (81%) among the patients with BVO ($p < 0.001$, Table 1). The history of upper back pain and cervical pain were more common in patients with TVO (p 0.016 and p 0.014, respectively) than in those with BVO and PVO. However, leg pain was more common among patients with PVO (p 0.003, Table 1). Urinary and defecation incontinence were reported in two patients with PVO and one patient with BVO. Haemoptysis was reported in one of the patients with TVO. Among 96 patients with BVO, 23 (24%) were diagnosed as having neurobrucellosis.

Among TVO cases, 25% had definite diagnosis, 21% probable diagnosis, and so 46% had definite or probable diagnosis. Among BVO cases, all were considered to be definite diagnoses, whereas among PVO cases, 58% were diagnosed as definite or probable (Table 3). Distribution of bacterial agents were, six methicillin-sensitive *Staphylococcus aureus*, one methicillin-resistant *S. aureus*, two methicillin-resistant coagulase-negative *S. aureus* and two *Escherichia coli*. In urinary culture, a total of 11 aetiological agents were isolated, one *Salmonella* Virchow, seven *E. coli*, (four

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TABLE 1. Demographic and epidemiological features

	Brucella vertebral osteomyelitis *n* = 96 (%)	Tuberculous vertebral osteomyelitis *n* = 63 (%)	Pyogenic vertebral osteomyelitis *n* = 55 (%)	p
Female gender	57 (59)	28 (44)	28 (51)	0.173
Mean age (SD; min–max)	53 (16; 13–81)	43 (18; 14–77)	53 (15; 20–83)	<0.001
Consumption of fresh cheese	81 (84)	17 (27)	18 (33)	<0.001
Dealing with husbandry	62 (65)	8 (13)	9 (16)	<0.001
History of spinal surgery	11 (11)	8 (13)	35 (64)	<0.001
Diabetes mellitus	14 (15)	12 (19)	18 (33)	0.028
Mean days between onset of symptoms and establishment of diagnosis	115 (SD 98, min 10, max 365)	266 (SD 43, min 7, max 1460)	151 (SD 264, min 10, max 1800)	<0.001
Symptoms				
Fever	67 (70)	33 (52)	37 (67)	0.069
Sweating	78 (81)	36 (57)	24 (44)	<0.001
Loss of appetite	66 (69)	40 (63)	26 (47)	0.031
Weight loss	59 (61)	36 (57)	19 (35)	0.005
Headache	27 (28)	13 (21)	8 (15)	0.144
Cough	5 (5)	6 (10)	4 (7)	0.578
Low back pain	90 (94)	55 (87)	52 (95)	0.248
Upper back pain	14 (15)	20 (32)	8 (15)	0.016
Cervical pain	3 (3)	10 (16)	4 (7)	0.014
Leg pain	47 (49)	33 (53)	42 (76)	0.003
Inability to walk	21 (22)	16 (45)	26 (47)	0.003
Arthralgia	29 (30)	4 (6)	1 (2)	<0.001
Physical examination				
Body temperature >38°C	24 (25)	13 (21)	14 (25)	0.776
Hepatomegaly	39 (41)	8 (13)	10 (18)	<0.001
Splenomegaly	15 (16)	1 (2)	2 (3)	0.003
Orchitis	3 (3)	0 (0)	0 (0)	NA
Neck rigidity	2 (2)	2 (3)	1 (2)	0.867
Arthritis	5 (5)	2 (3)	0 (2)	0.223

TABLE 2. Laboratory findings

	Brucella vertebral osteomyelitis *n* = 96 (%)	Tuberculous vertebral osteomyelitis *n* = 63 (%)	Pyogenic vertebral osteomyelitis *n* = 55 (%)	p
Leucocyte count				
<4000/mm^3	8 (8)	5 (8)	0 (0)	<0.001
4000–10 000/mm^3	74 (77)	44 (70)	29 (53)	
>10 000/mm^3	14 (15)	14 (22)	26 (47)	
Polymorphonuclear leucocytes (>75%)	10 (10)	20 (32)	20 (36)	<0.001
Lymphocytes (>45%)	14 (15)	1 (2)	0 (0)	<0.001
Monocytes (>9%)	26 (27)	16 (25)	7 (13)	0.111
Platelet <150 000/mm^3	3 (3)	4 (6)	1 (2)	0.395
Haemoglobin <10 g/L	23 (24)	19 (30)	24 (44)	0.041
Haematocrit <35%	41 (43)	30 (48)	37 (67)	0.013
Median erythrocyte sedimentation rate	50	44	70	<0.001
Median C-reactive protein	29	29	70	0.002
Elevated alanine transaminase >40 U/L	26 (27)	7 (11)	10 (18)	0.045
Elevated aspartate transaminase >40 U/L	22 (23)	13 (21)	9 (16)	0.631
γ-glutamyl transferase >50 U	46 (48)	19 (30)	22 (40)	0.083
Albumin	19 (20)	19 (30)	24 (44)	0.009
Globulin	52 (55)	31 (50)	30 (55)	0.825
Rheumatoid factor	8 (8)	2 (3)	2 (4)	0.293
TST ≥ 10 mm	23 (24)	54 (86)	26 (47)	<0.001
TST ≥ 15 mm	7 (7)	34 (54)	3 (5)	<0.001

extended-spectrum β-lactamase positive), one *Klebsiella* spp., one *Enterococcus faecalis*, one methicillin-resistant *Staphylococcus epidermidis*. In stool culture, in one patient *Salmonella* Group C was isolated. In decubitis culture among the patients with PVO, in two patients *Klebsiella* spp., *Acinetobacter* and *Pseudomonas* spp. were isolated.

For TST >15 mm, sensitivity was 0.66, specificity was 0.97, positive predictive value was 0.89, negative predictive value was 0.88, and receiver operating characteristic area was 0.8. The same parameters for TST >10 mm were 0.93, 075, 0.62, 0.96, and receiver operating characteristic area was 0.82. In multivariate analysis, TST >15 mm predicted TVO significantly (OR = 16, 95% CI 7.32–37.86; p <0.001, Table 4).

Among the patients with TVO, cervical involvement (p 0.023) and thoracic involvement (p 0.018) were more common than in the other patients. Among the patients with BVO, lumbar involvement was significantly more common than in the other patients (p <0.001). Discitis was detected in 86 (90%) patients with BVO, 45 (71%) patients with TVO, and 43 (78%) patients with PVO (p 0.013). Abscess was detected in 78 (81%) patients with BVO, 52 (83%) with TVO and 49 (89%) with PVO (p 0.438). Psoas abscess was detected in 13 of 96

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TABLE 3. Serological and bacteriological findings

Brucella vertebral osteomyelitis	*n* = 96 (%)
Culture	35 (35)
Blood	35 (35)
Cerebrospinal fluid	1
Synovial fluid	1
Serological tests	
Serum tube agglutination (STA) ≥100	95 (99)
Median STA	800
STA with CoomBVO (STA) ≥100	95 (99)
Median STA with CoomBVO	400
Tuberculosis vertebral osteomyelitis	*n* = 63 (%)
Culture	16 (25)
Acid fast stain	11 (6)
Pathological findings specific for tuberculosis (caseous, granulomatous)	10 (6)
Culture negative PCR positive	2
TST ≥15	34 (54)
Pyogen vertebral osteomyelitis	*n* = 55 (%)
Culture	
Blood	11 (20%)
Surgical material	14
Urine	11
Stool	1

TABLE 4. Multivariate analysis for brucellar, tuberculous, and purulent vertebral osteomyelitis among 214 patients

	OR	95% CI	p
Brucellar vertebral osteomyelitis			
Consumption of fresh cheese	5.4	2.22–12.9	<0.001
Dealing with husbandry	4.4	1.82–10.93	0.001
Sweating	3.2	1.41–7.18	0.005
Arthralgia	6.2	1.72–22.24	0.005
Hepatomegaly	3	1.08–6.65	0.033
Alanine transaminase >40 IU	3.1	1.25–7.44	0.014
Lumbar involvement in MRI	3	1.17–8.3	0.023
Tuberculous vertebral osteomyelitis			
Thoracic involvement in MRI	2.5	1.02–6.25	0.044
TST > 15 mm	16	7.32–37.86	<0.001
Pyogenic vertebral osteomyelitis			
History of spinal surgery	14.7	6.54–32.89	<0.001
Leucocytosis	5.4	2.43–12.14	<0.001

patients with BVO (13.5%), 18 of 63 patients with TVO (28.5%), and 12 of 55 patients with PVO (22%, Table 5).

Median days of non-specific antibiotic therapy before diagnosis of tuberculosis were 35 days (10–351). Median days of parenteral antibiotic therapy for BVO were 21 days (5–31), for TVO 27 days (10–169) and for PVO 35 days (14–563). Median days of oral antibiotic therapy for BVO were 180 days (7–561), for TVO 360 days (60–720) and for PVO 144 days (14–420).

In multivariate analysis, consumption of fresh cheese, dealing with husbandry, sweating, arthralgia, hepatomegaly, alanine transaminase >40 IU, lumbar involvement in MRI were found to be predictive for BVO; thoracic involvement in MRI and TST >15 mm were found to be predictive for TVO; history of spinal surgery and leucocytosis were found to be predictive for PVO (Table 4).

TABLE 5. Magnetic resonance image findings in patients with brucellar, tuberculous, and purulent vertebral osteomyelitis

	Brucellar vertebral osteomyelitis *n* = 96 (%)	Tuberculous vertebral osteomyelitis *n* = 63 (%)	Pyogenic vertebral osteomyelitis *n* = 55 (%)
Involved vertebra levels			
Cervical	4 (4)	7 (11)	1 (2)
Thoracic	8 (8)	15 (24)	9 (16)
Thoracolumbar	7 (6)	11 (17)	8 (15)
Lumbar	58 (60)	23 (37)	23 (42)
Lumbosacral	19 (20)	7 (11)	14 (25)
Localization of abscess			
Paravertebral	30 (32)	15 (24)	17 (31)
Epidural	19 (20)	7 (11)	7 (13)
Epidural + paravertebral	15 (16)	12 (19)	13 (24)
Psoas	2 (8)	8 (13)	0 (0)
Paravertebral + psoas	6 (6)	6 (10)	4 (7)
Paravertebral + epidural + psoas	5 (5)	4 (6)	8 (15)

Discussion

Studies from northern Europe and North America reported pyogenic VO; however, the aetiologies of VO are not limited to pyogenic microorganisms in many other countries. In Turkey, as a country between Asia and Europe, the aetiological list of VO includes *Brucella* spp. and *M. tuberculosis* spp., as well. Specific microorganisms can be identified in fewer than half of the patients [6,7]. Hence, case management is made by synthesis of data on epidemiological, clinical, laboratory, and imaging studies. As one of the strong parts of this study, multivariate analysis was performed for each category of disease entity.

Mean number of days between onset of symptoms and establishment of diagnosis was greater among the patients with TVO (266 days) than the patients with BVO (115 days) or PVO (151 days, p <0.001, Table 1). This time interval was reported to be 2–12 months in previous reports [3,8,9]. Such a long period of time before diagnosis could be related to the low frequency of disease and non-specific nature of the symptoms, such as low back pain.

Fever as a symptom was detected in 50–70% of our patients, with the lowest rate among patients with TVO, although there was no statistical significance among the three groups (Table 1). Body temperature >38°C was detected in around one-quarter of the patients (Table 1). In previous studies, fever was reported in only about half of patients [10,11], and, fever was reported as less common in patients with TBO [12]; however, in our multivariate analysis sweating was found to be 3.2 times more common (OR = 3.2, 95% CI 1.41–7.18; p 0.005) among the patients with BVO than TVO or PVO (Table 4). Back or neck pain is common [3], but up to 15% of patients may be pain free [10]. In our study, low back pain was highly common among all patient groups, whereas upper back and cervical pain were found to be significantly more common among patients with TVO (Table 1), which was related to thoracic involvement in TVO (Table 4). In our study, leg pain was significantly more common among patients with PVO than those with BVO or TVO (Table 1). This could

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be related to more frequent involvement of the epidural space that was detected in MRI. Epidural involvement was detected more commonly among patients with PVO (51%) than patients with BVO (40%) or TVO (36%). Twenty-four percent of patients with BVO were diagnosed as having neurobrucellosis.

Among the inflammatory markers, erythrocyte sedimentation rate and C-reactive protein are sensitive markers for infection but lack specificity [10], leucocytosis is occasionally present [13]. In our study, erythrocyte sedimentation rate and C-reactive protein were found to be significantly higher among patients with PVO than those with BVO or TVO (Table 1). These findings were in parallel with another report; however, in that report C-reactive protein elevation in the PVO group was not found to be statistically significant [1]. The leucocyte count was reported to be one of the least useful among the inflammatory markers [10]; however, in multivariate analysis we detected leucocytosis as one of the significant predictors of PVO (OR = 5.4, 95% CI 2.43–12.14; p <0.001, Table 4).

In our study, the most common aetiological agent in PVO was *Staphylococcus* spp. In previous reports, *Staphylococcus* spp. were reported as the most common causative agent, varying from 20% to 84% [8,10,14–16], whereas Gram-negative rods were reported as causative agents in 7–33% of patients with PVO [13,15,16]. In our study, the most common agents were *E. coli*, *Klebsiella* spp. and *Salmonella* spp. These microorganisms were associated with urinary or gastrointestinal tract infections. The Wright agglutination test was useful in diagnosis of BVO; Wright agglutination was positive in 99% of patients with BVO, whereas the bacteria were isolated in only 39% of patients with BVO.

Tuberculin skin test sensitivity and specificity is influenced by the cut-off used. A higher cut-off will result in a higher specificity and a lower sensitivity for *M. tuberculosis* infection [17]. In our study, in multivariate analysis, TST >15 mm predicted TVO significantly (OR = 16, 95% CI 7.32–37.86; p < 0.001, Table 4). For TST >15 mm, sensitivity was 0.66, specificity was 0.97, positive predictive value was 0.89, negative predictive value was 0.88, and receiver operating characteristic area was 0.8. In regions with higher prevalence of tuberculosis, using TST with 15-mm cut-off could be useful in diagnosis of tuberculosis.

Magnetic resonance imaging is considered the modality of choice for the radiological diagnosis of VO [5,18]. It has a reported sensitivity of 96%, specificity of 93% and accuracy of 94% [10]. In multivariate analyses, lumbar level involvement was found to be significantly more common among patients with BVO; however, thoracic level involvement was found to be more common among patients with TVO (Table 4). Another study reported significance of thoracic level involvement for patients with TVO [1]. More common thoracic involvement in patients with TVO could be explained by more frequent involvement of lymph nodes and the pleura in pulmonary tuberculosis, from where bacteria can reach the vertebral bone through the lymphatic route. In patients with BVO, lumbar involvement was reported as the most common location [19]. Discitis was found to be more common among patients with BVO, but presence of psoas abscess was more common among patients with TVO (Table 5). Previous studies reported the relatively higher frequency of psoas abscesses among patients with TVO, by noting vertebral, intestinal or genitourinary infections as the potential source [2,20].

There is no standard choice of agents and standard duration for VO, yet. Median days of non-specific antibiotic therapy before diagnosis of tuberculosis were 35 days (10–351). Median days of parenteral antibiotic therapy for BVO were 21 days (5–31), for TVO 27 days (10–169), and for PVO 35 days (14–563). Median days of oral antibiotic therapy for BVO were 180 days (7–561), for TVO 360 days (60–720), and for PVO 144 days (14–420). In treatment of BVO, rifampicin plus doxycycline or ceftriaxone were given for 6 weeks to 6 months. In treatment of TVO, four drugs were given for the first 2 months of therapy, followed by two drugs for 10 months. In treatment of PVO, in addition to glycopeptides, fluoroquinolones, or a β-lactam antibiotic was given. Duration of therapy was adjusted according to the clinical condition and laboratory findings of the patient. In BVO, 85% of the patients received oral therapy, whereas additional surgical therapy was performed in TVO (56%) and PVO (47%, Table 6). In 73% of

TABLE 6. Treatment modalities for the patients with vertebral osteomyelitis

	Brucellar vertebral osteomyelitis *n* = 96 (%)	Tuberculous vertebral osteomyelitis *n* = 63 (%)	Pyogenic vertebral osteomyelitis *n* = 55 (%)	p
Medical treatment	85 (89)	19 (30)	24 (44)	<0.001
Medical + percutaneous drainage of abscess	5 (5)	5 (7)	1 (2)	
Medical + surgical	6 (6)	35 (56)	27 (47)	
Medical + surgical + percutaneous drainage of abscess	0	4 (6)	3 (5)	
Number of surgical operations				
Once	3 (3)	32 (51)	22 (40)	<0.001
Twice	3 (3)	3 (5)	3 (5)	
Three or more	0 (0)	4 (6)	4 (7)	

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patients with BVO, 84% of patients with TVO and 62% of patients with PVO were cured. Overall, 25% of the patients were lost to follow up. One patient with BVO (1%), and two patients with PVO (4%) relapsed.

Conclusion

Tuberculous and brucellar VO remained the leading causes of VO with delayed diagnosis. In differential diagnosis of VO, consumption of fresh cheese, dealing with husbandry, sweating, arthralgia, hepatomegaly, elevated alanine transaminase and lumbar involvement in MRI were found to be predictors of BVO, thoracic involvement in MRI and TST >15 mm were found to be predictors of TVO, and history of spinal surgery and leucocytosis were found to be predictors of PVO.

Transparency Declaration

The authors declare no conflict of interest.

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